

Alpha-7 Nicotinic Receptor Agonists and Statins In Combination

Field of Invention:

This invention is concerned with the treatment of neurological degenerative diseases
5 and particularly with the treatment of Alzheimer's disease.

Background

The etiology of Alzheimer's disease is complex and not entirely understood. Current
hypotheses point to the overproduction of the amyloid peptide A β as a causative factor in the
cognitive deficits and neurodegeneration associated with Alzheimer's disease (Selkoe, 2001;
10 Walsh *et. al.*, 2002). In addition, epidemiological studies have shown that
hypercholesterolemia is a risk factor for Alzheimer's disease (Jarvik *et. al.*, 1995; Notkola *et.*
al., 1998). Further, it has recently been shown that the administration of statins is associated
with a decreased risk of Alzheimer's disease (Jick *et. al.*, 2000; Wolozin *et. al.*, 2000). Still
further, another recent study has shown that the statin lovastatin reduced A β plasma levels in
15 human subjects that had elevated plasma levels of low-density lipoprotein cholesterol
(Buxbaum *et. al.*, 2002).

Alpha-7 nicotinic receptors (α 7-nAChR) are ligand-gated ion channels that allow for
the entry into cells of calcium and other monovalent cations (Dani, 2001). α 7-nAChR have
been shown to play an important role in regulating neurotransmitter release, hippocampal
20 synaptic function, neuroprotection against a variety of insults, and cognition (Dani, 2001;
Dahas-Bailador *et. al.*, 2000; Rezvani and Levin, 2001).

Recent studies imply an interaction between A β and α 7-nAChR that may contribute to
the pathophysiology of Alzheimer's disease. A β has been shown to potently inhibit α 7-
nAChR (Liu *et. al.*, 2001). It has been proposed that this inhibitory effect of A β on α 7-
25 nAChR function may contribute to cognitive deficits in Alzheimer's disease.
Neurodegeneration induced by the activation of NMDA glutamatergic receptors is also
enhanced in the presence of A β (Kihara *et. al.*, 2001). This A β induced neurodegeneration is
inhibited by activation of α 7-nAChR.

Background References:

30 Buxbaum JD, Cullen EI and Friedhoff LT: Pharmacological concentrations of the
HMG-CoA reductase inhibitor lovastatin decrease the formation of the Alzheimer beta-
amyloid peptide in vitro and in patients. *Frontiers in Bioscience* 7:a50-a59, 2002.

Dajas-Bailador FA, Lima PA and Wonnacott S: The $\alpha 7$ nicotinic receptor subtype mediates nicotine protection against NMDA excitotoxicity in primary hippocampal cultures through a Ca^{2+} dependent mechanism. *Neuropharmacology* 39:2799-2807, 2000.

5 Dani JA: Overview of nicotinic receptors and their roles in the central nervous system. *Biol Psychiatry* 49:166-174, 2001.

Kihara T, Shimohama S, Sawada H, Honda K, Nakamizo T, Shibasaki H, Toshiaki K, and Akaike A: $\alpha 7$ Nicotinic receptor transduces signals to phosphatidylinositol 3-kinase to block A β -amyloid-induced neurotoxicity. *J Biol Chem* 276:13541-13546, 1998.

10 Jick H, Zornberg GL, Jick SS, Seshadri S, and Drachman DA: Statins and the risk of dementia. *Lancet* 356:1627-1631, 2000.

Jarvik GP, Wijsman EM, Kukull WA, Schellenberg GD, Yu C and Larson EB: Interactions of apolipoprotein E genotype, total cholesterol, age, and sex in prediction of Alzheimer's disease. *Neurology* 45:1092-1096, 1995.

15 Liu Q, Kawai H and Berg DK: b-Amyloid peptide blocks the response of $\alpha 7$ -containing nicotinic receptors on hippocampal neurons. *Proc Natl Acad Sci* 97:10197-10202, 2001.

Notkola IL, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, Kivinen P, Tuomilehto J and Nissinen A: Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. *Neuroepidemiology* 17:14-20, 1998.

20 Rezvani AH and Levin ED: Cognitive effects of nicotine. *Biol Psychiatry* 49:258-267, 2001.

Selkoe, DJ: Alzheimer's disease: Genes, proteins, and therapy. *Physiological Reviews* 81:741-766, 2001.

25 Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, and Selkoe, DJ: Naturally secreted oligomers of amyloid β protein potently inhibit hippocampal long-term potentiation in vivo. *Nature* 416:535-539, 2002.

Wolozin B, Kellman W, Ruosseau P, Celesia GG, and Siegel G: Decreased prevalence of Alzheimer's disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arch Neurol* 57:1439-1443, 2000.

30 **Description of the Invention:**

We have discovered that statins and $\alpha 7$ -nAChR agonists in combination have the potential to alter the pathophysiology of Alzheimer's disease and symptoms. The different mechanisms by which statins and $\alpha 7$ -nAChR agonists operate — statins by reducing the

formation of the neurotoxic substance A β and α 7-nAChR agonists by blocking the cognitive impairing and neurotoxic effects of A β — imply that a statin and an α 7-nAChR in combination will synergistically benefit patients suffering with neurological degenerative diseases and particularly patients suffering with Alzheimer's disease.

5 In one aspect the invention is a method for treating neurological degenerative diseases and particularly Alzheimer's disease comprising treatment with a combination comprising an α 7-nAChR agonist and a statin.

A combination suitable for practicing the invention comprises a statin selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin sodium, simvastatin or
 10 rosuvastatin, or a pharmaceutically-acceptable salt thereof and an α 7-nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,
 (+)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,
 (-)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,
 spiro[1-azabicyclo[2.2.1]heptan-3,5'-oxazolidin-2'-one],
 15 3'-methyl spiro-[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one],
 spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 20 1'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline],
 5'-(phenylcarboxamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 25 5'-(phenylsulfonylamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 5'-N-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 5'-N,N-dimethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 30 5'-N,N-diethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 5'-N-ethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
 5'-N-benzylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

- 5'-N-formamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-N-acetamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline],
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]quinoline],
5 5'-ethenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(E)-(phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-
b]pyridine],
5'-(4-morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(1-azetidiny)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
10 5'-(E)-(2-(4-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-
b]pyridine],
5'-(E)-(2-(2-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-
b]pyridine],
5'-(2-trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-
15 b]pyridine],
5'-ethynylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(2-furyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-(3-pyridyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
5'-methylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
20 spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5' carbonitrile],
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5' carboxamide],
5'-N'-(3-chlorophenyl)aminocarbonylminospiro[1-azabicyclo[2.2.2]octane-3,2'-(
(3'H)-furo[2,3-b]pyridine],
5'-N'-(2-nitrophenyl)aminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(
25 (3'H)-furo[2,3-b]pyridine],
4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
4'-methoxyspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
4'-phenylthiospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
4'-(N-2-aminoethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-
30 b]pyridine],
4'-phenylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
4'-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

- 4'-(4-N-methylpiperazin-1-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],
- 4'-chloro-spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine],
- spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine],
- 5 spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide],
- spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-6'-carbonitrile],
- 6'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine],
- 6'-fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine],
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide),
- 10 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),
- 15 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide),
- 20 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide),
- 25 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furan-2-yl)furan-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide),
- 30 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide),

- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);
5 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide),
10 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-
15 carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide),
20 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-
carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide),
25 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-
carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide),
30 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide),
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide),

- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide),
- 5 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide),
- N*-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide),
- 10 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide),
- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide); *N*-
- 15 (1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide),
- 20 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);
- 25 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide),
- 30 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide),
- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide),

- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide),
5 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide),
10 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide),
15 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-
carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide),
20 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-
carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-
carboxamide),
25 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-
carboxamide),
30 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-
carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide),
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide),

(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)[5-(4-chlorophenyl)furan-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-
5 carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinoliny)thiophene-2-carboxamide),
(S)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);
(S)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),
(S)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),
10 *(S)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-
15 carboxamide),
(R)-*N*-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholiny)phenyl)thiophene-2-
20 carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-
carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ,
25 *(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-
carboxamide),
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide), or
(R)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-
carboxamide), or a pharmaceutically-acceptable salt thereof.

30 In general, it is contemplated that any statin when used in combination with any
alpha-7-nAChR agonist will be useful in practicing the present invention.

Alpha-7-nAChR agonists contemplated to be useful in the present invention are
described in international publications WO9606098, WO9730998, WO 9903859,

WO9956745, WO0042044, WO0129034, WO0160821, WO0132622, WO0136417, WO0132619, WO0132620, WO0136417, WO0244176, WO0220521, WO0216358, WO0216357, WO0216356, WO0216355, WO0215662 and WO0217358 and in publications EP1219622, EP1184383, EP1184384, EP1184385, JP200203084. Statins contemplated to be
5 useful in the present inventions are atorvastatin calcium (Lipitor), cerivastatin sodium (Baycol), fluvastatin sodium (Lescol), lovastatin (Mevacor), pravastatin sodium (Pravachol), simvastatin (Zocor) and rosuvastatin (Crestor).

In another aspect the invention is a pharmaceutical composition comprising a combination of an $\alpha 7$ -nAChR agonist and a statin as described herein together with a
10 pharmaceutically-acceptable diluent or excipient.

In another aspect the present invention comprises providing neuroprotection or analgesia in a method of treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and
15 Parkinson's disease which method comprises administering a therapeutically effective amount of a combination as defined in Claim 1 to a patient.

In a particular aspect the method of the invention is a method for the treatment or prophylaxis of Alzheimer's disease.

A further aspect of the invention is the use of a combination of an $\alpha 7$ -nAChR agonist and a statin as described herein in the preparation of a medicament for providing
20 neuroprotection or analgesia in the treatment of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease.

In a particular aspect the use of a combination of an $\alpha 7$ -nAChR agonist and a statin as described herein is in the preparation of a medicament for the treatment or prophylaxis of Alzheimer's disease.

A particular combination for use in the present invention comprises rosuvastatin or a pharmaceutically-acceptable salt thereof and an $\alpha 7$ -nAChR agonist selected from spiro[1-
30 azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof.

A particular pharmaceutical composition for use in the present invention comprises rosuvastatin or a pharmaceutically-acceptable salt thereof and an $\alpha 7$ -nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof together with a
5 pharmaceutically acceptable diluent or carrier.

A particular method of the present invention is the provision of neuroprotection or analgesia for the treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders,
10 anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease. which method comprises administering a therapeutically effective amount of a combination of rosuvastatin or a pharmaceutically-acceptable salt thereof and an $\alpha 7$ -nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt
15 thereof to a patient. In particular the method is useful for the treatment or prophylaxis of Alzheimer's disease.

A particular embodiment of the invention is the use of a combination rosuvastatin or a pharmaceutically-acceptable salt thereof and an $\alpha 7$ -nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof in the preparation of a
20 medicament providing neuroprotection or analgesia for the treatment of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease. In particular the invention comprises the use of such a combination in the preparation of a medicament for the treatment of Alzheimer's disease.

Statins are compounds that inhibit HMG-CoA reductase, a rate-limiting enzyme in the biosynthetic pathway to cholesterol. Statins are conventionally used to reduce plasma levels
30 of cholesterol in patients with cardiovascular disease but can also reduce A β serum levels in patients. Alpha-7-nAChR agonists beneficially activate $\alpha 7$ -nACh receptors and are useful for treating cognitive deficits and in the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's disease, cognitive or attention disorders, anxiety,

depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease. Accordingly, the hypothetical basis of the present invention lies in the realization that statins, by reducing the formation of A β , may be particularly effective in combination with α 7-nAChR agonists, which ameliorate cognitive deficits and inhibit neurodegeneration induced by A β , in the treatment of Alzheimer's disease. Therefore, the treatment of Alzheimer's disease with a combination of a statin and an α 7-nAChR agonist will result in enhanced efficacy over either type of agent if administered alone.

Experimental:

Assessment of the efficacy of a statin and an α 7-nAChR agonist in combination in animal models is not straightforward. Existing experimental models of Alzheimer's disease include transgenic mice, which over express A β , and animals with surgically generated fimbria-fornix lesions. These models and the uses to which they may be put are known, understood and appreciated by those of skill in the relevant art. Transgenic mice which over express A β exhibit some of the clinical manifestations of Alzheimer's disease, *e.g.*, plaque deposition and, in some cases, cognitive deficits, but neurodegeneration is not observed. Animals with fimbria-fornix lesions have cognitive and learning deficits and have been used to assess potential approaches to treat neurodegeneration. No single experimental model exhibits the entire pathophysiological complex of Alzheimer's disease. However, to the extent that these models do mimic the pathophysiology of Alzheimer's disease they may be used to assess the effect of a statin and an α 7-nAChR agonist in combination.